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CHITOSAN-COUPLED SLNs AS MUCOADHESIVE DRUG DELIVERY SYSTEMS

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Riassunto

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Solid lipid nanoparticles (SLNs) are frequently used for biomedical purposes because of their biocompatibility and biodegradability. SLNs with positive surface charges possess mucoadhesive properties, because of the formation of an electrostatic interaction with the negatively charged groups on the mucus layer, providing an intimate contact between the drug delivery system and the site of application/absorption and prolonging the residence time at the target site [1]. In this work, chitosan, a positively charged polysaccharide, was used as a coating for SLNs to improve their biological interaction. High shear homogenization and ultrasound technique were employed to produce three different types of SLNs: Naked SLNs, chitosan-associated SLNs (CH-SLN), and SLNs coated with chitosan (CH-c-SLNs) [3]. The aqueous phase (water with surfactants - Tween 80 and Pluronic F68) was added into the melted lipid phase (Compritol 888 ATO and cyclosporin A) under homogenization (T25, IKA-Werke GmbH, Germany). Chitosan was added into the aqueous phase during SLNs preparation (CH-SLN) or after hot emulsification of SLNs (CH-c-SLNs). Nile red was dissolved into the lipid phase to investigate SLNs intracellular uptake. SLNs morphology and particle size were studied by means of cryo transmission electron microscope Glacios (Thermo Fisher Scientific) and dynamic light scattering (Litesizer 500), respectively. The results showed that spherical nanodroplets, having a mean particle size of about 180 nm, were obtained. In addition, particle-size distributions were analyzed by means of field flow fractionation (FFF Multiflow AF2000). Moreover, the thermodynamic interaction between SLNs and mucin was investigated by isothermal titration calorimetry at 37°C (MicroCaL PEAQ-ITC, Malvern) to assess the physiological and biological response. At this purpose, SLNs were freeze-dried and dispersed in acetate buffer 20 mM at pH 4.5. The nanoparticle dispersion with a concentration of 1 mg/ml was placed in the syringe and was added into the thermostated cell containing a suspension of mucins in acetate buffer (0.1 mg/ml). A plateau, corresponding to the equilibrium of the system, was reached for CH-SLNs and CH-c-SLNs, meaning that saturation of mucin by the SLNs occurs. In fact, the dissociation constant (Kd) of naked SLNs was higher compared to that obtained for SLNs containing chitosan, indicating a lower binding affinity. SLNs cytocompatibility was also assessed using the MTT assay on Raw 264. 7 macrophages. Each sample was put in contact with the cell substrates at different concentrations (ranging from 25 to0.05% v/v) for 3 hours. Results showed that the naked-SLNs and the CH-SLNs are more biocompatible compared to the CH-c-SLNs. Confocal laser scanning microscopy was performed to image the cellular uptake of SLNs after 3 hours of contact with each sample at 5%. The micrographs showed that SLNs were successfully internalized.
In conclusion, CH-SLN proved to possess enhanced mucoadhesive properties and this is a favorable feature to optimize cell uptake.

References: [1] Tan, S.L.J.; Billa, N. Improved Bioavailability of Poorly Soluble Drugs through Gastrointestinal Muco-Adhesion of Lipid Nanoparticles. Pharmaceutics 2021, 13, 1817. [2] Jung, H. Y., Le Thi, P., HwangBo, K. H., Bae, J. W., & Park, K. D. Tunable and high tissue adhesive properties of injectable chitosan-based hydrogels through polymer architecture modulation. Carbohydrate polymers 2021, 261, 117810.

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